PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D | A2

(11) International Publication Number: **WO 98/27058**

(43) International Publication Date: 25 June 1998 (25.06.98)

(21) International Application Number: PCT/EP97/07160

(22) International Filing Date: 15 December 1997 (15.12.97)

(30) Priority Data:

9626376.9	19 December 1996 (19.12.96)	GB
9700902.1	17 January 1997 (17.01.97)	GB

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). KING, Francis, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(54) Title: NOVEL COMPOUNDS

(57) Abstract

Novel carboxamide derivatives having CNS activity, processes for their preparation and their use as medicaments.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

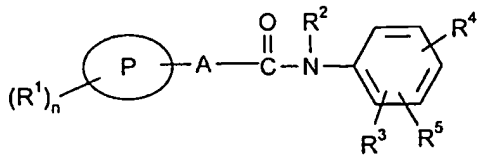
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL COMPOUNDS

This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

EPA 0 021 580 and EPA 0 076 072 describe sulphonamide derivatives which are disclosed as having antiarrhythmic activity. A structurally distinct class of compounds has now been discovered, which have been found to have $5HT_6$ receptor antagonist activity. $5HT_6$ receptor antagonists are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease (enhancement of cognitive memory), sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome).

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6:

R^2 is C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched. As used herein the term aryl includes phenyl and naphthyl.

When P is a bicyclic heterocyclic ring suitable examples include benzothiophene, quinoline or isoquinoline. Suitable 5 to 7-membered heterocyclic rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrrolidinyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom. Suitable substituents for these rings include R^5 groups as defined above.

Preferably P is phenyl, thiophene, benzothiophene or naphthyl.

Preferably A is a single bond, an ethyl or -CH=CH- group. Most preferably A is a single bond.

When R^1 is a 5-7 membered heterocyclic or bicyclic heterocyclic ring suitable examples include those given within the description of group P. Preferably R^1 is halogen or C_{1-4} alkyl optionally substituted by one or more halogens, for example methyl or CF_3.

Preferably n is 0, 1, 2 or 3, particularly 1 or 2.

Preferably R^2 is C_{1-6} alkyl, in particular methyl or ethyl.

Suitably R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$. It will be appreciated that when R^3/R^5 groups are linked together the two groups must be attached to adjacent carbon atoms of the phenyl ring. Preferably R^3 is a group R^5 in particular hydrogen.

Preferably R^4 is meta with respect to the carboxamide linkage. Preferably X is a bond, p is 0 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring. The heterocyclic rings can be linked to the remainder of the molecule via a

carbon atom or, when present, a nitrogen atom. Optional substituents for these rings, which can be present on carbon and/or nitrogen atoms, include C_{1-6}alkyl, in particular methyl. More preferably R^4 is an optionally substituted piperazine. Most preferably R^4 is N-methylpiperazine or piperazine.

Preferably R^5 is C_{1-6}alkoxy, most preferably methoxy. Preferably R^5 is para with respect to the amide group.

Particular compounds of the invention include:
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl-4-phenylbenzamide,
4-Bromo-N-ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-N-propylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,N-dimethylbenzamide,
Naphthalene-2-carboxylic acid N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
3-Chlorobenzo[b]thiophene-2-carboxylic acid-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3-Bromothiophene-2-carboxylic acid-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
4-*tert* Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methylbenzamide,
3-Chlorobenzo[b]thiophene-2-carboxylic acid N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methyl amide
and pharmaceutically acceptable salts thereof.

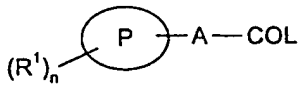
The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or

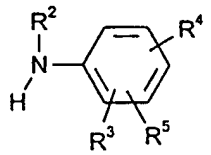
any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):



(II)

in which R^1, n, P, and A are as defined in formula (I) or protected derivatives thereof and L is a leaving group with a compound of formula (III):



(III)

in which R^2, R^3, R^4 and R^5 are as defined in formula (I) or protected derivatives thereof and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

Suitable leaving groups include halogen, in particular chloro. The reaction of a compounds of formulae (II) and (III) is carried out by mixing the two reagents together, optionally in an inert solvent such as dichloromethane.

Those skilled in the art will appreciate that it may be necesary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formulae (II) and (III) are commercially available or may be prepared according to known methods or analogous to known methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_6$ receptor antagonists are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease and enhancement of cognitive memory, sleep

disorders (including disturbances of Circadian Rhythym), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be

either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of compounds of the invention.

Example 1

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl-4-phenylbenzamide

A solution of biphenyl-4-carboxylic acid chloride in acetone (2ml) was added to a solution of N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylamine (1 equivalent) in acetone and the mixture stood overnight at room temperature. The resultant crystalline solid was filtered off and washed with acetone, then diethyl ether, to afford the title compound as the hydrochloride salt. MS: m/z = 416 (MH^+).

The following compounds were prepared in a similar manner from an N-alkyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amine and the appropriate carboxylic acid chloride:

	MS (MH^+)
4-Bromo-N-ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzamide (E2)	446/448
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-N-propylbenzamide (E3)	460/462
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,N-dimethylbenzamide (E4)	432/434
Naphthalene-2-carboxylic acid N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide (E5)	390
3-Chlorobenzo[b]thiophene-2-carboxylic acid N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide (E6)	430/432
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide (E7)	418/420
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide (E8)	408/410
3-Bromothiophene-2-carboxylic acid N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide (E9)	424/426
4-tert Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide (E10)	396
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide (E11)	418/420

Example 12

3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methylbenzamide (E12)

A solution of 1-chloroethylchloroformate (1.12mmol), 3,4-dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide (E8) (0.22mmol) and diisopropylethylamine (1.14mmol) in 1,2-dichloroethane (2ml) was refluxed for 12h. The solution was concentrated to a residue which was re-dissolved in methanol and refluxed for 6h. The mixture was concentrated, and the residue partitioned between dichloromethane and aqueous sodium bicarbonate solution. The organic layer was dried, concentrated to a residue and purified by column chromatography on silica gel using a methanol/dichloromethane solvent gradient. The hydrochloride salt of the title compound (E12) was prepared by dissolving the pure material from chromatography in acetone/dichloromethane and acidifying with ethereal HCl. MH^+ 393/395/397.

Example 13

3-Chlorobenzo[b]thiophene-2-carboxylic acid N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methyl amide (E13)

The title compound was prepared from 3-chlorobenzo[b]thiophene-2-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]methyl amide (E6) according to the method described for Example 12. MH^+ 415/417.

Method for assay of 5-HT6 antagonistic activity:

The test compounds were dissolved in polyethylene glycol:dimethyl sulphoxide (1:1) at 1 or 10mM and diluted to 0.1mM using 5mM tris buffer (pH 7.7 @ 25°C). Dissolution was assisted by addition of 0.02ml 5M HCl plus heating to 40°C and sonication for 10 minutes. Serial dilutions of drugs in the same buffer were carried out using either a TECAN 5052 or Biomek 2000 Workstation. Samples of the diluted test compounds (0.05ml) were mixed with 0.05ml of radio-ligand [^{3}H]-LSD prepared in the incubation buffer, and 0.4ml of a suspension of a preparation of the washed membranes of HeLa_5HT6 cells (acquired from Dr. D. Sibley, NIH, Bethesda, see Ref 1)(see Table 1), also in the incubation buffer. The details of the incubation conditions for each assay are shown in Table 2. The incubation buffer was 50mM Trizma (Sigma, UK) pH7.7 @ 25°C, 4mM $MgCl_2$.

After incubation at 37°C, the mixtures were filtered using a Packard Filtermate in Packard TopCount format. Filters were washed with 4 x 1ml aliquots of ice-cold incubation buffer. Filters were dried and impregnated with 0.04ml of Microscint 20 (Packard). IC_{50} values were estimated from the counts per minute using a four parameter logistic curve fit within EXCEL (2). K_i values were calculated using the method of Cheng and Prusoff (3). pIC_{50} and pK_i are the negative log10 of the molar IC_{50} and K_i respectively.

Table 1 Details of the methods used to prepare membranes for binding assays

1st resuspension cells/ml	spin / resuspension 1, 2 ,3	Incubation before final spin	protein conc. in stored aliquots	cells /ml in stored aliquots
7×10^7	Yes	20min at 37°C	4mg/ml	1.0×10^8

Table 2 Summary of receptor binding assay conditions

protein (ug/ sample)	radio-ligand [^{3}H]-LSD (nM)	Specific Activity (Ci/mmol)	Non-Specific Definition	Kd (nM)
40	2.0	83	Methiothepin	3.1

References

1. MONSMA, F.J., SHEN, Y., WARD, R.P., HAMBLIN, M.W., SIBLEY, D.R.. 1993. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.*, 43, 320-327.

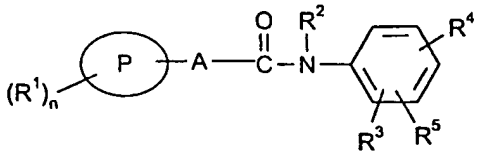
2. BOWEN, W.P., JERMAN, J.C.. 1995. Nonlinear regression using spreadsheets. *Trends in Pharmacol. Sci.*, **16**, 413-417.

3. CHENG, Y.C., PRUSSOF, W.H.. 1973. Relationship between inhibition constant (Ki) and the concentration of inhibitor which causes 50% inhibition (IC50) of an enzymatic reaction. *Biochem. Pharmacol.*, **92**, 881-894.

The compounds of Examples all showed good selective 5-HT6 receptor antagonist activity, having pKi values above 7.0 at human cloned 5-HT6 receptors.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or di C_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6:

R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)_p-R^6$ where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

2. A compound according to claim 1 in which P is phenyl.

3 A compound according to any one of claims 1 to 2 in which R^2 is C_{1-6}alkyl.

4 A compound according to any one of claims 1 to 3 in which R^4 is an optionally substituted piperazine ring.

5. A compound according to any one of claims 1 to 4 in which R^5 is C_{1-6}alkoxy.

6. A compound according to any one of claims 1 to 5 in which n is 1 or 2.

7. A compound according to claim 1 which is:

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl-4-phenylbenzamide,
4-Bromo-N-ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-N-propylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,N-dimethylbenzamide,
Naphthalene-2-carboxylic acid N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
3-Chlorobenzo[b]thiophene-2-carboxylic acid-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3-Bromothiophene-2-carboxylic acid-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methyl amide,
4-*tert* Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-N-methylbenzamide,
3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methylbenzamide, or
3-Chlorobenzo[b]thiophene-2-carboxylic acid N-(4-methoxy-3-piperazin-1-ylphenyl)-N-methyl amide,
and pharmaceutically acceptable salts thereof.

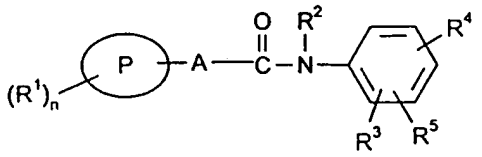
8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A compound according to any one of claims 1 to 7 for use in therapy, in which the beneficial activity is effected by antagonism of 5-HT6 receptors.

10. A compound according to any one of claims 1 to 7 for use in the treatment of schizophrenia, Alzheimer's disease and/or depression.

11. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

12. A process for the preparation of a compound of formula (I) or a salt thereof



(I)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, alkylamino or dialkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6:

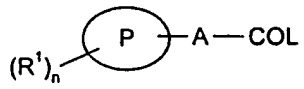
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

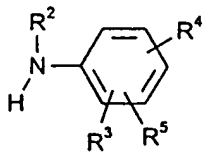
R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl;

which process comprises the coupling of a compound of formula (II):



(II)

in which R^1, n, P, and A are as defined in formula (I) or protected derivatives thereof and L is a leaving group with a compound of formula (III):



(III)

in which R^2, R^3, R^4 and R^5 are as defined in formula (I) or protected derivatives thereof and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 409/ 12, A61K 31/495, C07D 295/12 // (C07D 409/12, 333:00, 241:00)

A3

(11) International Publication Number: **WO 98/27058**

(43) International Publication Date: 25 June 1998 (25.06.98)

(21) International Application Number: PCT/EP97/07160

(22) International Filing Date: 15 December 1997 (15.12.97)

(30) Priority Data:

9626376.9	19 December 1996 (19.12.96)	GB
9700902.1	17 January 1997 (17.01.97)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). KING, Francis, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
20 August 1998 (20.08.98)

(54) Title: N-PIPERAZIN-1-YLPHENYL-BENZAMIDE DERIVATIVES

(57) Abstract

Novel carboxamide derivatives having CNS activity, processes for their preparation and their use as medicaments.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 97/07160

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D409/12 A61K31/495 C07D295/12 //(C07D409/12,333:00, 241:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17888 A (SMITHKLINE BEECHAM CORP ;DAINES ROBERT A (US)) 6 July 1995 see page 47; example 25 ---	1
X	WO 95 11243 A (SMITHKLINE BEECHAM PLC ;JOINER GRAHAM FRANCIS (GB); GASTER LARAMIE) 27 April 1995 see examples 1,2,4,9,11 ---	1,10
X	GB 2 276 165 A (GLAXO GROUP LTD) 21 September 1994 see interm. 22; examples 8,20,33,37,40,41,44,45,46 ---	1,10
X	WO 95 04729 A (SMITHKLINE BEECHAM PLC ;DUCKWORTH DAVID MALCOLM (GB); JENKINS SARA) 16 February 1995 see desc. 3-7; examples 1-12,14-18 ---	1,10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 May 1998	03. 07. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 276 164 A (GLAXO GROUP LTD) 21 September 1994 see examples 1-4,6,8	1,10
X	EP 0 533 267 A (GLAXO GROUP LTD) 24 March 1993 see interm. 4,7,8,9,11,18,25,26,32,33,37,44,49,51,59; examples 1-22	1,10
X	GB 2 273 930 A (GLAXO GROUP LTD) 6 July 1994 see examples 8-15	1,10
X	EP 0 533 266 A (GLAXO GROUP LTD) 24 March 1993 see example 5	1,10
X	WO 94 15920 A (GLAXO GROUP LTD ;CARTER MALCOLM (GB)) 21 July 1994 see interm. 4,6	1
A	WO 94 21619 A (PFIZER ;CHENARD BERTRAND L (US); MACOR JOHN E (US); SEGELSTEIN BAR) 29 September 1994 see claims	1-11
A	EP 0 661 266 A (TOA EIYO LTD) 5 July 1995 see claims	1-11
A	FR 2 699 533 A (MOUHTARAM MOHAMED ;JUNG LOUIS; KOFFEL JEAN CLAUDE; STAMBACH JEAN F) 24 June 1994 see claims	1-11
A	CHEMICAL ABSTRACTS, vol. 100, no. 21, 21 May 1984 Columbus, Ohio, US; abstract no. 174780, XP002066493 see abstract & R. AGARWAL ET AL.: INDIAN J. PHARMACOL., vol. 14, no. 2, 1982, pages 177-182,	1-11

-/--

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 97/07160

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 121, no. 7, 15 August 1994 Columbus, Ohio, US; abstract no. 73080, XP002066494 see abstract & J.W. CLITHEROW ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 15, 1994, WASHINGTON US, pages 2253-2257, & DATABASE CHEM. ABS. REGISTRY American Chemical Society see RN: 156428-83-0, 156428-86-3 ---	1-11
A	WO 94 01556 A (INST NAT SANTE RECH MED ;AMLAIKY NOURDINE (FR); BOSCHERT URSULA (F) 20 January 1994 see page 10 - page 11 -----	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/07160

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1

Vague terms/expressions like "heterocyclic" or "optionally substituted" do not allow to specify the scope of claim 1 for which a protection is sought. The search had to be restricted for economical reasons (see Guidelines for Examination in EPO, B-III, 2). Consequently the search was limited to the general idea underlying the application in the frame of the scope illustrated by the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. tional Application No
PCT/EP 97/07160

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9517888	A	06-07-1995	AU	1441195 A	17-07-1995
			EP	0738144 A	23-10-1996
			JP	9507846 T	12-08-1997
			ZA	9410318 A	01-08-1995
WO 9511243	A	27-04-1995	EP	0724580 A	07-08-1996
			JP	9503773 T	15-04-1997
GB 2276165	A	21-09-1994	NONE		
WO 9504729	A	16-02-1995	EP	0712397 A	22-05-1996
			JP	9501171 T	04-02-1997
GB 2276164	A	21-09-1994	NONE		
EP 0533267	A	24-03-1993	AU	2452892 A	25-03-1993
			AU	2568792 A	27-04-1993
			CA	2078507 A	19-03-1993
			CN	1073430 A	23-06-1993
			CZ	9400611 A	16-11-1994
			WO	9306084 A	01-04-1993
			FI	941261 A	17-03-1994
			JP	6107637 A	19-04-1994
			MX	9205278 A	01-03-1993
			NO	940974 A	17-03-1994
			US	5358948 A	25-10-1994
			ZA	9207106 A	17-03-1994
GB 2273930	A	06-07-1994	NONE		
EP 0533266	A	24-03-1993	AU	2452992 A	25-03-1993
			CA	2078506 A	19-03-1993
			CN	1071922 A	12-05-1993
			FI	924159 A	19-03-1993
			HU	66319 A	28-11-1994
			JP	6107649 A	19-04-1994
			MX	9205279 A	01-03-1993
			US	5356893 A	18-10-1994
			ZA	9207107 A	08-09-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
PCT/EP 97/07160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9415920 A	21-07-1994	AU 5815594 A	15-08-1994
		CN 1094037 A	26-10-1994
WO 9421619 A	29-09-1994	AU 6391894 A	11-10-1994
		CA 2158457 A	29-09-1994
		EP 0689536 A	03-01-1996
		FI 941213 A	17-09-1994
		HU 67312 A	28-03-1995
		JP 8503228 T	09-04-1996
		ZA 9401806 A	15-09-1995
EP 0661266 A	05-07-1995	JP 7242629 A	19-09-1995
		US 5728835 A	17-03-1998
FR 2699533 A	24-06-1994	NONE	
WO 9401556 A	20-01-1994	FR 2693201 A	07-01-1994
		CA 2139431 A	20-01-1994
		EP 0651802 A	10-05-1995
		JP 7508655 T	28-09-1995